REMARKS

To expedite prosecution of the application, Applicants submit the following remarks and arguments with the accompanying Request for Continuing Examination.

Status of claims

Claim 12 has been amended to recite "[a] method for the treatment or prophylaxis of chronic fatigue syndrome in a mammalian patient characterized by an excessive level of, *or excessive sensitivity to*, IL-6 cytokines in said patient, which method comprise . . ." Italics added.

Support for the amendment can be found in Applicants' specification at, for example, page 9, line 23 – page 10, line 3. Claim 12 has also been amended to correct minor grammatical errors.

Claim 18 has been amended to correct its dependency from canceled Claim 9 to pending Claim 17. This dependency reflects that original Claim 9 is now canceled.

No new matter has been added by these amendments.

Following amendments, Claims 12-18 will remain pending in the application.

The above amendments are entered solely to clarify the claimed invention and to expedite allowance of what is believed to be allowable subject matter. Applicants reserve the right to file a continuation application directed to the previously presented claims.

Summary of the claimed subject matter

A single independent method claim (Claim 12) and six dependent claims (Claims 13-18) are pending in the application.

The claims are drawn to a method for the treatment and/or prophylaxis of chronic fatigue syndrome (CFS), a disease associated with elevated levels of the proinflammatory cytokine, IL-6, and other cytokines. Specification at, *e.g.*, page 2, lines 23-28 and page 9, lines 20-28. The method involves the extracorporeal application of thermal, oxidative, and UV light stresses to a patient's blood, followed by reintroduction of the stressed blood to the patient. Reintroduction of the stressed blood brings about various beneficial effects including a reduction in the levels of the IL-6 cytokine. See, *e.g.*, page 1, line 20 – page 2, line 12; page 2 lines 14-22; and page 3, lines 17-21.

Specifically, independent Claim 12 is drawn to a method for the treatment or prophylaxis of chronic CFS in a mammalian patient, characterized by an excessive level of or excessive sensitivity to the IL-6 cytokine. The method comprises the steps of:[1]

(i) selecting a patient suffering from or at risk of suffering from CFS;

(ii) withdrawing blood cells from the patient;

(iii) subjecting the blood cells to extracorporeal oxidative and ultraviolet light stress; and

(iv) administering an effective amount of the stressed blood cells to bring about the reduction of the levels of IL-6 cytokines in the patient.

The language of Claim 12 is supported by the specification. For example, the use of stressed blood cells to treat CFS, and for the prophylaxis of CFS, is disclosed at, *e.g.*, page 2, lines 23-28 and page 9, lines 20-23.

Patient selection, as in (i), is based on the clinical presentation of symptoms of CFS, or indicia of risk of developing CFS, as described at, *e.g.*, page 2, lines 23-28 and page 9, line 20 – page 10, line 3.

[1] Step numbers do not appear in the pending claims but are provided for the Examiner's convenience in this section of the Amendment and Reply and are not intended as a limitation to the claims.

Withdrawing blood cells from a patient, as in (ii), and reintroducing stressed blood cells, as in (iv), are described at, *e.g.*, page 4, lines 9-28.

The step of subjecting the blood cells to a combination of extracorporeal oxidative and ultraviolet light stress, as in (iii), is described, *e.g.*, at page 4, lines 24-28 and page 7, lines 9-11, with oxidative and ultraviolet stress being described throughout the application, *e.g.*, at page 5, line 28 – page 7, line 17.

The reduction of IL-6 cytokines in response to the administration of stressed blood cells, as in (iv), is described at page 2, lines 14-21 and page 3, lines 17-21.

The subject matter of the dependent claims is also disclosed in the specification. For example, the additional use of heat stress, applied simultaneously with oxidative and ultraviolet stress, as recited in Claim 13, is described, *e.g.*, at page 4, lines 24-28; page 5, lines 7-9; page 8, lines 14-17; and page 10, lines 25-28.

The oxidative conditions recited in Claim 14 and 15 are described at, *e.g.*, page 5, line 28 – page 6, line 20; page 7, lines 18-19; and page 11, lines 3-11.

The use of UV-C ultraviolet light (*i.e.*, wavelengths of less than 280 nm), as recited in Claim 16, is described at, *e.g.*, page 6, lines 21-27 and page 11, lines 3-8.

The use of a heat stressor in the range of from about 40 to about 55°C, as recited in Claim 17, is described at *e.g.*, page 5, lines 10-24; page 8, lines 20-22; and page 11, lines 3-8.

The use of a volume of whole blood of from about 0.1 to about 400 mls, as recited in Claim 18, is described at, *e.g.*, page 4, lines 11-17 and page 10, line 28 – page 11, line 3.

Rejections

I. Claims 12-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled for the treatment or prophylaxis of CFS.

II. Claims 12-18 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over WO 98/07463 or U.S. Patent No. 5,980,954 or WO 00/06703, each in view of the CDC Report (1999).

Arguments

I. Enablement Rejection under 35 U.S.C. § 112, first paragraph

Claims 12-18 were rejected under 35 U.S.C. § 112, first paragraph, because the specification is allegedly not enabling for a method of treatment or prophylaxis of chronic fatigue syndrome (CFS). Office Action of August 26, 2004 at paragraph (¶) 5 and Advisory Action of February 25, 2005 at ¶ 1.

Applicants will separately address the various parts of the rejection, as set forth in the Office Action of August 26, 2004 at ¶ 5.

A. The specification is enabling for the treatment of chronic fatigue syndrome

The standard for enablement is whether "one reasonably skilled in the art could make or use the invention . . . without undue experimentation." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Here, the Office Action and Advisory Action acknowledged that the specification *is enabling* "for a process of decreasing expression of . . . IL-6." ¶¶ 5 and 1, respectively. Accordingly, the Patent Office appears to be satisfied that the underlying biology behind the claimed methods is adequately supported by the specification and satisfy the conditions of 35 U.S.C. § 112.

Applicants submit that the specification is also fully enabling for the application of these methods to the treatment and/or prophylaxis of CFS. By simply following the guidance provided in the specification, one skilled in the art could readily apply the teachings of the specification to the treatment and/or prophylaxis of CFS, without undue experimentation.

The specification explicitly identifies CFS as a disorder associated with excessive amounts of IL-6 and/or increased sensitivity, thereto. See, *e.g.*, page 2, lines 23-28 and page 9, lines 23-28. This assertion is supported by a series of references, which appear at the bottom of page 9. While evidence of record suggests that additional factors may be involved in the etiology of CFS, it does not refute (nor does the USPTO) that CFS is associated with elevated IL-6 and/or enhanced sensitivity thereto. This provides the basis for the methods of this invention in treating CFS with stressed blood cells, as claimed.

As to the lack of a working example, rejection of claims because of the absence of such an example is inconsistent with well-established Patent Law and inconsistent with the Patent Office's own guidelines on the subject. According to the M.P.E.P. at 2164.02:

> [t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure . . . [t]o make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.

Even if, *arguendo*, the claimed invention did *not* prove effective in treating CFS (which Applicants expressly do not concede) it would still *not* require undue experimentation to make this determination. One need only follow the teachings of the specification and monitor the progress of the CFS patient.

Moreover, in addition to overstating the amount of experimentation necessary to treat CFS, the Patent Office has also failed to fully apply the guidelines set forth in *In re Wands*, 858

F.2d 731,737 (Fed. Cir. 1988), the case from which the "undue experimentation" standard is derived.

In re Wands identifies a number of factors to be considered in making an enablement rejection. Undue experimentation, the factor on which the Patent Office has based the rejection, is only one such factor. *In re Wands* also acknowledges that the *nature* of the invention has bearing on the enablement question. Here the nature of the invention is that the administration of extracorporeally-stressed blood cells will produce a general decrease in the levels of IL-6 cytokine, which is associated with CFS. Properly applied, the Wands factors take this feature of the invention into account.

Only by reducing the Wands factors to a simple question of "undue experimentation," in the absence of any context for the inquiry, then overstating the amount of experimentation necessary, does the Patent Office escape the inevitable conclusion that the specification is enabling for the full scope of the claims.

B. Prophylaxis versus Treatment

The Office Action at page 4 (first full paragraph) alleges that the specification is not enabling for methods of prevention/prophylaxis, as opposed to treatment[2]. However, methods of prevention, as well as treatment, are enabled by the specification. The specification states, at the bottom of page 2 (lines 24-26), that the "process of the invention is useful in the medical treatment of patients suffering from, *prone to, or at risk of contracting* a disorder associated with excessive amounts of . . . and IL-6" (italics added). The specification also states that the "invention is particularly indicated for *prophylaxis* or alleviation of chronic fatigue syndrome (CFS) in human patients." Page 9, lines 22-23 (italics added). The methodology for treatment is the same as that for prophylaxis, which is fully disclosed in the specification. Moreover, there would appear to be no basis for distinguishing between *treatment* and *prophylaxis*, in terms of

[2] These arguments were reiterated in the Advisory Action of February 25, 2005.

compliance with the enablement requirement, particularly since the relevant characteristics of the patient, *i.e.*, presenting with elevated levels of IL-6, or sensitivity to IL-6, are explicitly recited in independent claim 12. The levels of IL-6 are clearly measurable as evidenced by the measurement of IL-6 mRNA levels in the Example, which results are shown in Figure 2.

Thus prophylaxis/prevention, as well as treatment, of disorders associated with excessive levels of IL-6, are enabled by the specification, or by the specification combined with the knowledge of those skilled in the art.

C. Animal models and undue experimentation

The Office Action asserts that there is no animal model for CFS and that it would be unpredictable how to correlate the data obtained in mice with *in vivo* results. ¶ 5 (bottom of page 3). Restated, this question turns on whether the description of the treatment of mice is enabling for the treatment of humans.

Applicants assert that U.S. patent law has never required the disclosure of studies in humans to support claims drawn to the treatment of humans. There is simply no statutory basis nor case law precedent that requires Applicants to provide an animal model to satisfy 35 U.S.C. § 112. All that was alleged in this rejection were the unsubstantiated allegations of the Examiner to which Applicants take issue. Absent appropriate evidence by the USPTO, an unsubstantiated allegation is insufficient to maintain the rejection.

D. Conclusions with respect to the enablement rejections

To the extent that this rejection is predicated on a skepticism of the *utility* of the claimed invention, such skepticism is not a basis for an *enablement* rejection.

The specification describes a methods for stressing and reintroducing blood, which is then useful for treating a variety of disorders, including CFS. Since practicing the claimed

invention in treating CFS is disclosed in the specification, it is simply incorrect to assert that undue experimentation is necessary to practice the invention in the treatment or prophylaxis of CFS. Claims 12-18 are fully enabled by the specification and the outstanding enablement rejection should be withdrawn.

To support an enablement rejection, the Patent Office must offer objective evidence, *e.g.*, in the form of a prior art reference or Declaration by the Examiner, which can be then be rebutted by the Applicants. Here the Patent Office has issued only unsupported conclusions with respect to the alleged lack of enablement. This leaves Applicants with no recourse, since the rejection is based on allegations that Applicants can neither refute nor rebut. If the Patent Office maintains the outstanding enablement rejection, it must provide a factual basis and allow Applicants to respond to the evidence.

II. Obviousness rejection under 35 U.S.C. § 103

Claims 12-18 were rejected under 35 U.S.C. § 103 as allegedly being obvious over WO 98/07463, U.S. Patent No. 5,980,954, or WO 00/06703 in view of a certain CDC Report.

The Office Action states at page 6, ¶ 7, that an obviousness rejection cannot be overcome by attacking the references individually. However, U.S. patent law has never precluded an Applicant from arguing against a combination of references, based on the teachings of the individual references. Here, the traversal is on the grounds that one skilled in the art would not be motivated to combine the cited references.

A. No motivation to combine

In re Vaeck requires the Patent Office to show some motivation for combining references to support an obviousness rejections. 947 F.2d 488 (Fed. Cir. 1991). Here, it is not clear why one skilled in the art would combine the CDC reference with two references that disclosed methods for modulating immune function with stressed mammalian blood. There is no nexus to connect

these references and motivate one skilled in the art to make the combination. The mere fact that references can be combined is not sufficient to support an obvious rejection. *In re Mills*, 916 F.2d. 680 (Fed. Cir. 1990). Here, the Patent Office has failed to establish any basis for making the combination.

Specifically, the Office Action at page 7 (first full paragraph) acknowledges that "the above references are silent about the fact that [the] disease condition in a patient is mediated by excess inflammatory cytokine production . . . *i.e.*, IL-6."[3] This statement is significant because it is the association of CFS with elevated levels of IL-6 or excessive sensitivity to IL-6 cytokines that make the methods of the invention applicable to treating and/or preventing CFS.

The Patent Office appears to rely on the CDC reference to make the connection between the administration of stressed mammalian blood and the treatment and/or prevention of CFS. However, the CDC reference does not teach that "CFS is an inflammatory disease mediated by excess inflammatory cytokine production," at stated in the Office Action at page 7 (third paragraph from bottom)[4]. Instead, the CDC article lists a number of "Possible Causes" for CFS (*i.e.*, "Virus," Immune Response," "Infection and Inflammation," Endocrine System," Chemical Sensitivity," Mental Sensitivity," and Oxidative Stress"). Pages 6-7, capitalization in original. While the CDC article at page 10 discusses inflammatory cytokines in the context of "[a] theory published by Dr. Martin L. Pall," the article does not adopt this theory. It merely presents it as one of several theories that may explain CFS.

B. Conclusion with respect to obviousness rejection

Particularly in view of the limited value of the CDC reference in establishing CFS disease etiology, the Patent Office has not established why one skilled in the art would have combined

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[3] See also page 3 of the Advisory Action of February 25, 2005.

[4] Note that independent claim 12 has been amended to recite "[a] method for the treatment or prophylaxis of chronic fatigue syndrome in a mammalian patient characterized by an excessive level of *or excessive sensitivity to*, IL-6 cytokines in said patient, which method comprise . . ." Italics added.

the teachings of the CDC reference with the other cited references to produce the instant invention. Applicants submit that the Patent Office has failed to establish a *prima facie* case for obviousness and that the outstanding obviousness rejection must be withdrawn.

CONCLUSION

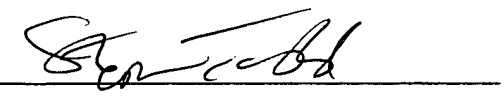
Applicants believes that the present application is in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: April 20, 2005

By 

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